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NUTRITION REVIEWS

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NUTRITION REVIEWS

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NUTRITION IN INTERNMENT CAMPS IN THE FAR EAST

Sensational statements have appeared in the press from time to time regarding the treatment of allied nationals in civilian internment camps in Japan and in territory occupied by the Japanese armed forces. In such reports some reference has usually been made to the supply of food, but the amounts of recorded data on this subject are very limited.

A list of food materials furnished at the Stanley Camp at Hongkong during the first six months of 1942 is given by Laird (*Nutrition Reviews* **1**, *97* (*1943*)). Among the American and Canadian repatriates returning from the Far East on the exchange ship Gripsholm in the fall of 1943 was a group of physicians and nurses who arranged a discussion on shipboard on the nutritional situation in the internment camps. The clinical observations made on this occasion are being prepared for publication elsewhere. Kramer (*J. Am. Dietet. Assn.* **20**, *213* (*1944*)) reports a dietary study carried out in 1943 in connection with a kitchen which served 400 internees. The following account includes data gathered on the Gripsholm and concerns most of the internment camps in the Far East. The author was one of about 1800 allied nationals interned in North China at Camp X.

About a dozen internment camps were set up by Japan for the concentration of allied nationals, mainly British and American. These camps, by a certain euphemism, were termed by the Japanese authorities "Civilian Assembly Centers." In all cases the internal administration was in the hands of the internees. This included not only so-called "activities," but also all services involving the physical welfare of the interned community, such as food preparation, medical care, and sanitation in all its aspects. In several camps this included pumping the water and digging drainage ditches. Each camp community promptly organized; committees were appointed, and the work was divided so that each individual had a labor assignment of from two to four hours a day. Unusual skills were developed; college professors became bakers, and bankers became sanitary experts. The smallest of the camps housed about 50 internees, the largest about 4000.

The Japanese authorities furnished food materials after the pattern of an occidental diet and according to a fixed schedule which varied, however, in the different areas, not only in variety but also in the quantity supplied per capita. In two of the camps, instead of supplying the food materials, funds were furnished to the committees who were then permitted to make food purchases. In these cases, while an attempt was made to build up a balanced diet, there were always limitations in the food materials available; many food items had disappeared from the market.

After supplying the raw food material, the Japanese authorities were not concerned with the manner in which it was cooked or distributed. It was possible, therefore, to make dietary studies or estimates of the caloric intake without interference from the camp authorities. Equipment for weighing was not of the best, and accurate data on the nutritive value of the food materials used were not always available. Except in one or two cases it was not possible for internees boarding the repatriation steamer to bring with them printed records or written memoranda. Most of the data included in this report were committed to memory by the individuals concerned and later put into writing. The author desires to acknowledge

a debt of gratitude to the many who collaborated in collecting these data.

Table 1 records the food materials furnished in Camp X, the quantities being in grams of raw food material as furnished, expressed as averages per capita per day over a period of three months. It was generally acknowledged that the food supplied Camp X was more liberal than that supplied some of the other camps. The figure for the meat ration given in this table is subject to a reduction of 20 to 25 per cent on account of spoilage. Table 2 is a summary of the data reported in Kramer's study for one of the kitchens in Camp X. Table 3 comprises data for several other camps, calculated on the basis of food materials supplied. It should be noted that in the case of Camps V and W, the food committee was permitted to secure Red Cross supplies and to make extra purchases from a special camp food fund. In some of the camps it was possible for individuals to purchase limited amounts of food materials from the canteen. At Camp X this included small amounts of peanuts and peanut oil and also fruit occasionally; each individual was entitled to purchase 1 egg every other day. Fruit was not generally supplied as part of the camp ration. During the spring months, the author at this camp was able to purchase 1 orange at the canteen every two or three weeks. A small amount of milk was available in some of the camps and was usually reserved for infants and invalids. At most camps a black market sprang into being, operating over the wall or through the barbed wire. Operations on the black market were attended with considerable risk to both seller and purchaser, but to the individual with private resources it brought much needed relief in the form of eggs, sugar, fruit, and sometimes meat. Many of the British internees found the low meat ration particularly distressing.

All observers agree that the factor of acceptability was of importance in defining the nutritive value of the diet or at least in determining the resultant benefit to the individual. All the kitchens were limited in equipment. In Camp X, there was approximately one large cauldron for each 200 people, and this was the only item of cooking equipment provided. All meals were served, therefore, in the form of a stew, and this continued day after day to be the principal item and usually the only item on the menu.

Only a few of the camps had dining rooms where internees could enjoy their meals with comparative comfort. Long waiting in queues was the rule, each individual armed with his own cup, plate, and spoon; most of the embellishments of life were lacking. Not only were there physical factors of impor-

TABLE 1

Ration, Camp X (Averages per capita per day)

	g.
Meat	140
Fish	22
Eggs	6
Bread	460
Flour	6
Margarine	6
Oil	11
Sugar	17
Jam	1
Potatoes	285
Vegetables	380
Coffee substitute	3
Tea	3

TABLE 2

Dietary Study, Camp X (Averages per capita per day)

	Calories	Protein	Calcium	Phosphorus	Iron
		g.	g.	g.	g.
Meat, fish, eggs	291	26	0.03	0.31	0.003
Flour	1210	39	0.08	0.34	0.004
Sugar	80				
Oils, fat	156				
Potatoes, roots, tubers	149	3	0.04	0.11	0.002
Leafy vegetables	19	2	0.10	0.05	0.004
Totals	1905	70	0.25	0.81	0.013

tance, but there were also psychologic factors, including that of morale, to be reckoned with. Isolation from families, severing of communications, life behind barbed wire, interruption of accustomed work and occupation—all these played a role in the health of the camp. The nutritional problems became in part psychologic ones. This may sound like a paradox, but careful observers in all the camps were constantly reminded of the intimate relationship of physical and psychologic factors. The determining factors were as often as not emotional ones.

It will be noted from the data in the tables that the caloric and protein intakes were generally below the accepted requirement. In addition to this, the calcium intake was low. This would be expected on a diet of milled cereals where the intake of protective foods was low. The food furnished was generally deficient also in thiamin, riboflavin, and ascorbic acid. The lack of calcium caused considerable anxiety. Supplies of calcium lactate were available in only some of the camps. Bone meal as a calcium supplement was not obtainable; meat furnished Camp X had already been carefully deboned by the authorities. It was arranged, therefore, in Camp X, to save all egg shells; these were collected, cleaned, pulverized, and administered to the children and adolescents in an attempt to meet the calcium deficiency. Cracked wheat from the Red Cross was secured by some of the camps, but in most camps whole cereals were not available.

The clinical reports from the camps which had been operating for only five or six months indicated some beriberi but no other outstanding nutritional deficiencies. There was, however, no special diagnostic equipment available, so that these reports comprise gross observations only. It would appear that the meat and carrots eaten were sufficient to meet vitamin A needs, while the occasional fruit supplied some vitamin C. In the case of those camps which had been operating for twenty months, beriberi and general symptoms of "vitamin B" deficiencies were common. Many persons experienced hunger for the first time, and considerable losses in body weight were reported, especially with those carrying the heavier labor assignments. Various types of intestinal disturbance were reported in all the camps; in several camps these reached epidemic proportions. An increasing number of individuals in those camps which had been operating for the longer period of time applied for treatment at the camp dental clinic, many of whom showed signs of decalcification. More detailed observations are included in the clinical report previously referred to.

The author's observations during intern-

TABLE 3

Nutritive Value of Ration for Different Camps

(Averages per capita per day)

Camp	Number of internees	Calories	Protein	Calcium	Phosphorus	Iron	Vitamin A	Thiamin	Riboflavin	Ascorbic acid
			g.	*g.*	*g.*	*g.*	*I.U.*	*mg.*	*mg.*	*mg.*
T	4000	1520	45	0.23	0.78	0.018	4,600	1.0	0.5	47
U	800	2195	80	0.44	1.34	0.029	12,000	1.5	1.0	87
V (a)	1100	1955	40							
V (b)	1100	2500	75							
W (a)	1650	1900								
W (b)	1650	2500	75							
Z	2500	1600	46	0.12						

(a) figures represent regular camp ration.

(b) figures represent ration (a) plus Red Cross supplement and extra purchases.

ment for six months in Camp X confirm his convictions that: (1) the factor of acceptability, with attendant psychologic factors, is of great importance in determining the effectiveness of an internment camp diet; (2) it is extremely difficult to arrange a properly balanced diet on an intake which quantitatively barely meets the caloric requirement; (3) most Americans and Europeans find it difficult to accommodate themselves to a monotonous low calory diet which is high in roughage and other materials that irritate the intestinal tract; (4) the recent recommendation of the Food and Nutrition Board, which sets the requirement for sedentary and moderately active individuals at 2500 and 3000 calories respectively, provides a commendable margin of safety and is not too high.

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SUPPLEMENTARY FEEDING IN PREGNANCY

A report by Balfour (*Lancet* **I**, *208 (1944)*) adds to the impressive fund of data accumulated during the past few years attesting to the importance of an adequate diet during pregnancy. In an experiment covering 10 areas in the north of England and 18 in South Wales, 11,618 pregnant women were given food supplements and their records compared with those of 8095 pregnant women, from the same areas, who did not receive these supplements. The author concludes that there was a significant reduction in the combined stillbirth and neonatal mortality rate. Maternal deaths in the series were too few for any conclusions to be drawn.

The experiment started in April 1937, and was concluded in March 1939. In the areas selected unemployment was acute and the unemployment benefit left no margin for extra food for the expectant mother. The women receiving the supplements were from the poorer classes. Women who attended the same prenatal clinic were used as controls. All cases of abortion and miscarriage were excluded and infant deaths during the first four weeks of life were counted as neonatal deaths. Once every two weeks each woman who was to receive supplementary food was given a pound and a half of a dried milk preparation and either 4 ounces of a yeast extract or 8 ounces of a proprietary preparation containing a rich supply of vitamins A and D and calcium, phosphorus, and iron. The controls were receiving milk from the local authorities so the main difference between the "fed" and control groups lay in the ingestion by the "fed" group of the yeast extract or the proprietary preparation. It was estimated that the amount of yeast extract distributed was sufficient to give the women 240 I.U. of B_1 each day and that the amount of the proprietary preparation supplied gave the women 13,500 I.U. of vitamin A and 2250 units of vitamin D per day.

The fed and control groups were compared as to parity, age, and social and economic conditions. Yerushalmy (*Am. J. Hygiene* **28,** *244 (1938)*) has shown that the neonatal death rate is influenced by the parity. It is least in the second confinement and begins to rise in the third. By the fifth it exceeds that of the first and at the tenth and subsequent confinements, the rate is nearly double that for primiparas. Yerushalmy also showed that the neonatal mortality rate rises with age in women over 30. In the present study there was found to be a higher proportion of primiparas in the control group but this was counterbalanced, from the point of view of equity in assessing results, by the much lower proportion of women with a parity of ten or more. In

regard to age, there was a smaller proportion of women over 30 in the control group. The women of the fed group were all in very poor circumstances, the wives of unemployed men or of low wage earners. Many were living under slum conditions, crowded and insanitary. There were many individual cases of hardship and distress. The women of the control class included some who were poor but most were of a better economic status. There was less overcrowding and where there were large families the provision of food for the children did not entail the great personal sacrifice demanded of the poorer mothers. The analysis of the two groups showed, therefore, that they were not strictly comparable but the scales were weighted against the fed group.

In analyzing the results, a difference was considered significant only when it would be produced by chance alone on fewer than 1 in 20 occasions. The cases receiving the preparation and those receiving yeast extract were considered separately. In the group where the mothers had received the proprietary preparation the neonatal and stillbirth mortality rate was lower than that of the controls but the difference was not statistically significant. In the groups where the mothers had received the yeast extract supplement, the neonatal and stillbirth mortality rate was significantly lower than the rate for the controls in both England and Wales. In the combined areas, too, the difference was striking, the likelihood of it arising by chance being less than 1 in 1300. The effect of the yeast extract was greatest in the areas where the control mortality rates were highest.

There were insufficient maternal deaths to permit accurate assessment of the effect of the supplementary feeding on the maternal mortality rate. From the analysis of the limited data available, it appears that the difference in the rate in the fed and control groups was not statistically significant.

Although no definite conclusions could be drawn on this point, the results of this study are in fundamental agreement with the results of studies previously reviewed in this journal (*Nutrition Reviews* **1,** *81, 276, 386 (1943)*). Perhaps the most striking feature of the present report is the fact that beneficial effects could be obtained from such a relatively small improvement in the diet. If, as seems probable, the author is correct in her belief that the main difference in the diets of the fed group, which responded best and its control group, was the yeast extract, then the benefit was brought about by approximately 8 g. of this concentrate for each of the expectant mothers daily. This represents a genuine contribution to the total thiamin and iron which they obtained and a lesser improvement in their riboflavin and niacin intake. There was no material increase, however, in certain other essentials such as ascorbic acid and vitamin A. This study makes a welcome addition to the available data concerning the desirability of improved diets during pregnancy.

PROTEIN RESERVES AND ANTIBODY PRODUCTION

Antibodies are apparently specifically modified globulins. Since the synthesis of normal globulin results from the utilization of dietary protein (Madden and Whipple, *Physiol. Rev.* **20,** *194 (1940)*), the probability exists that food protein also plays an important role in the production of antibody globulin. Several years ago Cannon (*Nutrition Reviews* **1,** *186 (1943)*) advanced this hypothesis and summarized those observations in the literature which gave it support. He also stated that experiments in his laboratory showed that rabbits whose protein reserves had been reduced by plasmapheresis and a low protein diet were less able to produce antibodies than were normal ani-

mals. Detailed description of these experimental results have now been published (Cannon, Chase, and Wissler, *J. Immunology* **47,** *133 (1943)*). Their implication is so great that they should be reviewed more completely.

Three series of experiments were performed, in each of which 16 rabbits were used. Half of the animals served as controls and were fed ad libitum a commercial rabbit food (Alpha Flakes) supplemented with 100 to 200 g. of carrots two or three times a week. This diet permitted young rabbits to grow normally and seemed to maintain good nutritional status of mature animals. The experimental rabbits were fed either carrots alone or, on alternate days, carrots and a synthetic ration composed of 37 per cent sucrose, 40 per cent corn starch, 3.5 per cent lard, 15 per cent "Ruffex" Fisher, and 4 per cent of a salt mixture. The synthetic diet contained only 85 mg. of nitrogen per 100 g., or a maximum of 0.5 per cent protein. No attempt was made to supplement the feedings with vitamins because the authors felt that those circumstances which would cause men to consume a diet inadequate in protein also usually provide a low vitamin intake; they wished to simulate these conditions. Daily, or on alternate days, 25 to 50 ml. of blood were removed from the left ventricle of those animals scheduled for plasmapheresis. After centrifugation the plasma was discarded, the red cells resuspended in Locke's solution and returned to the animal. In all, 150 to 200 ml. of plasma were removed, an amount equivalent to two or three times the total circulating protein. Determinations were made at regular intervals of the serum proteins, hematocrit, hemoglobin level, and red blood cell count.

In the first series of experiments, 16 young rabbits averaging 825 g. in weight and about 10 weeks of age were used. The 8 maintained on the low protein diet were fed 150 g. of raw carrots per day for twenty-four days. During this period their weight remained practically stationary. For the next twenty-five days they were given first 200 g. and then 250 g. of carrots per day. After that, and for the duration of the experiment, they were given 200 g. of carrots and 100 g. of the synthetic ration on alternate days. At the end of sixty-six days their weight was only slightly greater than it had been at the beginning of the period while the weight of the control group of animals had increased approximately two and a half times. An anemia had also developed in the low protein rabbits and the average serum protein had fallen from an initial average value of 5.89 g. per 100 ml. to 4.37 g. The serum protein in the control group, meanwhile, had risen from 6.17 to 6.66 g. per 100 ml. On the sixty-sixth day each animal was injected subcutaneously with 0.2 ml. of an Eberth. typhosa vaccine. At intervals of four, eight, and twelve days thereafter, serum was obtained for titration of agglutinins against the homologous vaccine. Average agglutinin output of the well fed rabbits was about five times greater than that of the protein depleted animals.

The second series of experiments were conducted in an almost identical manner and comparable results were obtained. However, one week after the final titration of agglutinins to the typhoid vaccine had been made, each animal was injected intravenously with a vaccine of Salmonella paratyphi. The material was given intravenously because it was felt that a more uniform distribution of the antigenic particles throughout the antibody-producing system might thereby be produced. In this instance also the average output of agglutinins was three to five times better in the control than in the depleted rabbits.

Adult rabbits were used for the third series because it was felt that dietary protein must be used by young animals partly for structural growth. When they are subjected to antigenic stimulation, therefore, a sort of competition might conceivably occur between the needs for growth and the needs

for synthesis of globulin. With a limited protein intake, the production of antibody globulin could conceivably be hampered. Older animals would not be subject to this objection. Consequently, the protein reserves of 9 adult rabbits were depleted by plasmapheresis, by feeding the low protein diet, or by a combination of the two. Serum proteins varied in these animals at the end of the depletion period from 4.97 to 6.87 g. per 100 ml. The values for the control group ranged from 6.62 to 7.77 g. Even though the degree of protein depletion, as judged from values for serum protein, was not so great as in the first two series, the experimental animals produced less antibody globulin than the controls by a factor of 2.5 to 5.

These observations leave little doubt that, under the conditions of protein depletion produced, antibody formation is defective in the rabbit which is, immunologically, a very sensitive animal. However, since the diets used in these experiments were probably deficient in many nutrients other than protein, additional studies should be done in which all of the known essential nutrients except protein are provided in adequate amounts. The authors state that such experiments have already been started. The role of protein deficiency as the specific factor responsible for the poor synthesis of antibodies would be more definitely established, furthermore, if young control animals were fed a high protein ration but only as many calories as were the young experimental rabbits so as to produce a comparable degree of malnutrition.

Nevertheless, as Cannon and associates point out, the serious food deprivations to which many people are subject during war usually are associated both with poor vitamin and poor protein intake. The greater incidence of infection and epidemics at these times, especially among civilian populations, "suggest the importance of famine and malnutrition as causes of decreased resistance." Antibody production is certainly an essential part of the body's defense against infectious disease. Demonstration of the importance of nutrition to the synthesis of antibody globulin is reason enough, from a practical point of view, for encouraging the plans for improvements in nutritional standards throughout the world.

It must be remembered that antibody response is not a measure of the resistance to infection—it implies that once infection has occurred bodily defenses are manifested to limit its extent—and that one part of these defenses is antibody production. Accordingly, the theory of protein intake and resistance to infection is not amply tested by antibody response alone.

SELF-SELECTION OF DIETS

The fact that an animal species survives is proof that under natural conditions the majority of animals of that species find and eat an adequate diet. This may be true because (1) natural foods are complex, and only with special selection can an animal obtain a diet lacking in any dietary essential; (2) the animals may select their food on the basis of physiologic needs; or (3) both these factors may contribute to the balancing of the diet.

Interest in the ability of animals to select food began when Evvard (*Proc. Iowa Acad. Sci.* **22,** *375 (1915)*) announced that pigs could select for themselves a balanced diet that allowed remarkably good growth. He believed, therefore, that the pig's appetite was a reliable indication of its physiologic need. In recent years, several investigators have attempted to determine how adequate a diet animals will select when given a choice of the ingredients of that diet. Furthermore, Davis (*Am. J. Dis. Child.* **36,** *651 (1928)*) found that 1 to 2 year old children selected an adequate diet from a wide choice

of natural foods, primarily because they preferred fruits, milk, and whole grain cereals to other foods. No refined foods were offered them, and a good share of the balance of their selections consisted of high protein foods—ground muscular and glandular meats, and eggs.

Osborne and Mendel (*J. Biol. Chem.* **35,** *19* (*1918*)) and Mitchell and Mendel (*Am. J. Physiol.* **58,** *211* (*1921*)) found that in certain cases rats or mice preferred an adequate diet to an inadequate one when offered a choice of two laboratory diets. However, their data were limited and in several cases the animals did not make a satisfactory selection, so that no convincing conclusion could be reached. Green (*Physiol. Rev.* **5,** *336* (*1925*)) reported that South African cattle from pastures whose soil was low in phosphorus had developed the habit of chewing bones. In severe cases, the cattle would chew tin cans, and sticks of wood. Thus, no specific appetite for phosphate was evident, but probably only a generalized hunger.

Beadles, Braman, and Mitchell (*J. Biol. Chem.* **88,** *615* (*1930*)) reported that rats could not distinguish (as determined by "refusals to eat" in paired feeding) a low protein diet deficient in cystine from the same diet made more adequate by the addition of cystine. Kon (*Biochem. J.* **25,** *473* (*1931*)) gave rats a definite amount of yeast extract and then allowed them to eat ad libitum from separate feeders containing casein, sucrose, or salt mixture. The rats chose a diet containing only 6.5 per cent protein, grew poorly, and 2 out of 6 died; control animals fed a stock diet of the same ingredients providing 20 per cent protein grew well. Harlow (*J. Genet. Psychol.* **41,** *430* (*1932*)) fed normal rats (previously fed on the McCollum standard diet) twice daily for one hour only and at that time allowed them to choose from four cups containing different foods. He recorded the number of times the animals ate from each cup and the total amount eaten. The animals selected the McCollum standard diet or meat scraps equally often, preferred these to cheese and showed least preference for corn. Rats made blind or anosmic or both had the same preferences. Animals which had been fed previously on corn, lettuce, and milk, however, showed a marked preference for meat over the standard diet. When previously fed on the McCollum diet plus lettuce, the rats showed a significant preference for the McCollum standard diet over meat scraps. Harlow concluded that while under his experimental conditions appearance and odor of food had no effect on appetite, the previous diet played a definite role in the animal's choice. It was apparent that only a slight change in this earlier diet (such as the introduction of lettuce) could have a definite effect.

Harris, Clay, Hargreaves, and Ward (*Proc. Roy. Soc.* **113B,** *161* (*1933*)) made the first comprehensive study of an appetite for a single dietary factor. They proved clearly that a preferential appetite for foods containing thiamin over thiamin free foods was developed during thiamin deficiency in rats, and that this was an educated appetite developed as a result of the immediate beneficial effects they experienced when eating the thiamin-containing food. The animals could not make a beneficial selection if (1) the thiamin content of the beneficial food was less than adequate, (2) too many foods (six to ten) were offered as choices, or (3) the thiamin after being in one food was transferred to another food with a different flavor. If the beneficial food contained a more than adequate amount of thiamin, the animals showed no distinct preference for it. If many foods were offered for choice and then the rat was allowed to eat only the thiamin-containing food for a short period so that he experienced its beneficial effects, the animal would eat no other food choices thereafter. His appetite was then considered "educated." Efforts by these workers to find or develop a comparable appetite for vitamin A, vitamin D, or protein were unsuccessful.

Franke and Potter (*Science* **83,** *330* (*1936*))

demonstrated that rats avoided diets containing selenium (as seleniferous wheat or sodium selenite) if other food was available. If no selenium-free food was available, the animals ate the seleniferous diet readily.

The existence of an appetite for salt in herbivorous animals has long been a common observation. Richter (*Am. J. Physiol.* **115,** *155* (*1936*)) found that rats, when adrenalectomized, increased their appetite for salt solution presumably because of the excessive loss of salt in the urine following operation. In addition, the voluntary intake of glucose decreased, while that of water increased (*Endocrinology* **29,** *115* (*1941*)). Hypophysectomy caused a decrease in salt intake, probably because of the lowered metabolic state of the animals. Richter believed that the appetite for salt was not a learned habit but an inherent physiologic characteristic because the salt taste threshold as determined by self-selection methods was different in normal and adrenalectomized animals (*Endocrinology* **24,** *367* (*1939*)), and because the rats no longer preferred salt solution after the taste buds had been denervated. This evidence is not clear, however, because thresholds obtained by self-selection may show only the salt concentrations the rats find important enough to modify their habits and not the true physiologic threshold of taste. Further, it is difficult to see how the rats would have any possible way of distinguishing salt solution from water if the taste buds were denervated. Mark (*Endocrinology* **31,** *582* (*1942*)) confirmed the fact that rats had an increased appetite for salt following adrenalectomy. He failed to find the changes in glucose or water intake that Richter reported.

Richter and Eckert (*Endocrinology* **21,** *50* (*1937*)) found that rats after parathyroidectomy usually had an increased appetite for calcium lactate.

Wilder (*J. Comp. Psychol.* **24,** *547* (*1937*)) noted that rachitic rats could not select the beneficial diet when offered a choice between a rachitic and an antirachitic diet. This was confirmed by Young and Wittenborn (*J. Comp. Psychol.* **30,** *261* (*1940*)).

Young (summarized in *Psychol. Bull.* **38,** *129* (*1941*)) studied from a psychologic standpoint the behavior of rats when confronted with a choice of foods. Certain of his observations have nutritional significance, however. Rats usually will sample all the possible choices before eating from the final choice. Certain rats will be spatially oriented so that they eat from only one cup regardless of what food is in it. Food preferences may change during the course of a meal or from day to day and preferences may depend on what was eaten before the choice is made or on what comprises the basal diet. Some rats have no preferences and eat at random. Most of Young's observations have been confirmed.

Jukes (*J. Comp. Psychol.* **26,** *135* (*1938*)) found that chickens suffering from riboflavin deficiency could not distinguish between a diet containing riboflavin and a similar diet which contained none. "Education" such as Harris *et al.* had used had no effect in determining a choice, nor did flavoring of one of the two choices. Chickens refused consistently to eat alfalfa meal (which contains riboflavin and vitamin A but has a bitter taste) even when suffering from a riboflavin or a vitamin A deficiency. The birds showed a pronounced position orientation and preferred to eat from the compartment in a corner of the cage.

Richter, Holt, and Barelare (*Am. J. Physiol.* **122,** *734* (*1938*)) showed that rats could select from feeders containing olive oil, casein, yeast, sucrose, wheat germ oil, cod liver oil, and a variety of salt solutions amounts of food such that normal growth and reproduction were maintained. When female rats were pregnant or lactating, all intakes of food were increased except those of sucrose and yeast (*Endocrinology* **23,** *15* (*1938*)). When yeast was omitted from the normal animal's choice, all food intakes decreased except the fat intake (*Am. J. Physiol.* **124,** *596* (*1938*)). Richter and Hawkes

(*Am. J. Physiol.* **131,** *639* (*1941*)) fed rats a series of B-vitamins alone and in various combinations and noted changes in the animals' appetites for protein, fat, carbohydrate, and salts. Their results were somewhat obscure because so many variables were involved, but the general appetite, as shown by an increase in total calories consumed, closely paralleled an increase in protein intake, an increase in weight gained, and an increase in salt intake. Carbohydrate and fat intakes showed no regularity.

An excessive craving for sugar is considered a typical symptom of diabetes, but Richter and Schmidt (*Endocrinology* **28,** *179* (*1941*)) reported an aversion to sugar in most of their pancreatectomized rats. One of their animals did have a marked appetite for sugar, eating 22 g. per day. When insulin was injected into normal rats (*Am. J. Physiol.* **135,** *781* (*1942*)), the animals' total caloric intake increased. This increase was in most cases accompanied by an enhanced sugar appetite. After injections were stopped many animals still ate more sugar than before insulin treatment. In the light of the work of Harris *et al.*, this continued preference for sugar may represent "education" of the animal's appetite for sugar.

In view of earlier work, papers by Clark and Clausen (*Am. J. Physiol.* **139,** *70* (*1943*)) and Warkentin, Warkentin, and Ivy (*Am. J. Physiol.* **139,** *139* (*1943*)) take on considerable significance. Clark and Clausen placed a group of rats in a single cage and offered them a choice of yeast, dextrose, casein, and salts in cups and 3 per cent sodium chloride, water, and olive oil-cod liver oil mixture in drinkers. (Attempts to duplicate Richter's experiments in which the rats selected a suitable salt mixture from several drinkers with one salt in each were unsuccessful.) In normal animals, a lowered sugar intake was associated with a higher fat intake, but the total caloric consumption was approximately constant. After adrenalectomy the salt appetite was increased and, confirming Mark, no change in glucose or total water consumption was noted. Subcutaneous implants of desoxycorticosterone acetate pellets in the adrenalectomized animals' shoulders decreased the salt appetite. Unfortunately, due to the conditions of the experiment, no data on individual rats were available.

Warkentin *et al.* attempted to determine in what manner experimental thyroid abnormalities would affect the appetites of rats. No differences in food choices were observed when rats were made hypothyroid or hyperthyroid, although the total calories consumed by animals in the three groups varied as would be expected. Certain of the authors' observations are worthy of note, however. When rats were offered their choice of casein, dextrin, lard, and a mixture of equal parts of yeast and salts, only 5 out of 13 animals selected successfully. The other 8 rats selected a diet containing only 5.5 per cent casein and 5.5 per cent yeast. The authors conclude that these rats did not eat enough yeast because of its salty taste and therefore lost appetite. It is apparent, however, that they selected more yeast than is present in the McCollum diet (3 per cent). These results are strikingly similar to those of Kon and suggest the interesting possibility that a yeast intake adequate for normal growth of rats on a standard diet is inadequate for suitable self-selection of diet.

When Warkentin *et al.* separated the yeast from the salts only 1 out of 20 rats failed to select successfully. Diets chosen by young rats consisted of 17 to 24 per cent casein, 38 to 54 per cent dextrin, 4 to 17 per cent lard, 16 to 24 per cent yeast, and 1 to 2 per cent salts. There was an obvious reciprocal relationship of fats and carbohydrates; protein intake, if it varied at all, varied with total calories consumed. After the age of about 120 days, the caloric intake per hundred grams of body weight was decreased, and this decrease was accomplished by a lower voluntary intake of fat and carbohydrate with little change in protein intake. These authors conclude that under their experimental conditions the rats "eat for calories."

It is convenient to define an appetite as the

desire to eat a given substance and, in all self-selection experiments, an appetite is indicated when one food is preferred over another. Appetites may be divided into three classes: (1) hungers, which are appetites based on physiologic need, (2) educated appetites, which are the result of beneficial experience, and (3) simple appetites, which include all appetites not otherwise listed. Simple appetites may be of trivial origin. In the first class belong the generalized hunger associated with lack of food, thirst, and possibly the salt appetite. The thiamin appetite studied by Harris *et al.* is of the second class. An example of the third class is the appetite of the rat for saccharin, discovered by Hausmann (*J. Comp. Psychol.* **15,** *419* (*1933*)). The appetite of rats for alcohol, also studied by Hausmann (*J. Comp. Psychol.* **13,** *279* (*1932*)), is probably a simple one. The position of other appetites is uncertain.

Certain generalizations on the study of appetite deserve special mention. To prove that an appetite is based on a physiologic need and therefore a true hunger, one must show that a change in the need produces a change in appetite and that learning through beneficial experience is not a factor. The fact that an animal selects foods from a series of containers and grows normally is not proof that he selects these foods on the basis of need, because under most experimental conditions, if the animal ate only at random, his needs would be well supplied. The existence of appetites for dietary factors needed in small amounts (e.g. vitamins) can not be proved by observing the response of a rat when placed in a cage with the pure factor, because the exploratory nibbling habit of the rat will allow a sufficient intake of the factor to supply his needs. Changes in intake of a given food do not imply a change in appetite if they are accompanied by parallel changes in intakes of other foods in the diet. Statistical tests of significance should be applied to all self-selection data.

It is evident from the experiments here reported that more comprehensive studies of various appetites are much needed at the present time. However, certain conclusions seem justified concerning the role of appetites in nutrition:

(1) Appetites are often fickle and unpredictable (cf. Davis, Harlow, Young).
(2) Appetites may be trivial in origin (cf. Hausmann).
(3) Nutrition based on appetites is not universally successful.
(4) Individual animals vary in their ability to make choices that will improve nutritional status.
(5) Factors affecting human appetites may be expected to be more numerous and more complex than those affecting the appetites of animals.
(6) From the evidence, self-selection of diets appears to be inferior to scientific evaluation of diets for the maintenance of good nutrition.

FEEDING FOR MAXIMUM VITAMIN A IN BUTTER

In 1940 Wilbur, Hilton, and Hauge published the first of a series of papers (*J. Dairy Sci.* **23,** *765* (*1940*)) in which they endeavored to establish the vitamin A requirement of dairy cattle for the production of milk fat of high vitamin potency. Two Guernsey cows were depleted of their vitamin A reserves and alfalfa hay was used as the source of vitamin A (carotene) to bring the vitamin potency of the butterfat back to a high level. They concluded that the dairy cow must receive approximately 550,000 units per day to produce a vitamin rich butter containing 30 or more Sherman-Munsell units of vitamin A per gram.

In the second report of this series (*J. Dairy Sci.* **27,** *57* (*1944*)), vitamin A in the form of a fish liver oil was fed instead of carotene. Guernsey cattle, in the early stage of lactation, were again employed as experimental

animals. The cows were maintained on a vitamin A deficient diet until the vitamin A content of the butter fell to a level of about 12 Sherman-Munsell units per gram. At this point each cow was fed daily doses of vitamin A at successive levels of 25,000, 50,000, 75,000, 100,000, and 200,000 units in successive feeding periods of twenty-one days each. During the first two feeding periods, in which the respective daily intakes of vitamin A were 25,000 and 50,000 respectively, the vitamin A content of the butter remained at the low level of about 10 to 12 units per gram. However, when 75,000 units were fed, a slight increase in the vitamin potency of the butter was noted. Not until the daily intake reached 100,000 units was it possible to bring the butter unitage up to 30. When 200,000 units were fed the butters reached maximum potency of about 35 vitamin A units per gram.

In a second feeding trial, 2 Guernsey cows were depleted as before. One cow was then started at a daily intake of 50,000 units and increased during successive twenty-one day feeding periods to 300,000 units per day, after which the daily doses were gradually reduced in succeeding periods until the daily intake was back to 50,000 units. The other cow was started at the high level (300,000 units) with descending doses to 50,000 units and then back to the 300,000 unit level during the final feeding period.

The butter did not reach 30 units per gram in the "low to high to low" feeding trials until the daily intake of halibut liver oil reached 150,000 units per day. Maximum unitage of butter (35 units per gram) was reached when the daily intake reached 300,000. As unit intakes became smaller, the vitamin potency of the butter also decreased.

However, when a cow received 300,000 units per day immediately following the depletion period, the butter reached its maximum (33 units per gram) almost immediately and fell gradually to 14 units per gram as the daily intake fell to 50,000 units. When the daily intakes were again increased to 200,000 units, the butter again increased in potency to 31 units per gram.

Thus it appears that daily intakes of approximately 200,000 units of vitamin A *per se* are required to produce a butter rich in vitamin A, while more than a half million units of vitamin A in the form of carotene are required to produce a similar result. Another observation of interest is the relative speed with which the butterfat responds to fish liver oil as compared to alfalfa hay. These results indicate that carotene is about one-third as effective as vitamin A for this purpose, which is in general agreement with the differences in effectiveness of these vitamin sources for sheep, cattle, and swine in the prevention of night blindness (Guilbert, Miller, and Hughes, *J. Nutrition* **13,** *543 (1937)*).

In the third and last report in this series, Hauge, Westfall, Wilbur, and Hilton (*J. Dairy Sci.* **27,** *63 (1944)*) compared the effectiveness of crystalline carotene with that found in alfalfa hay for the production of butters possessing high vitamin A activity. These experiments were identical with those just described except that Guernsey cows received variable intakes of carotene in the form of crystalline carotene (in oil) and a specially dehydrated alfalfa hay of high carotene content. The carotene values were determined spectrophotometrically. Chromatographic separations were made of alpha and beta carotenes and the crystalline carotene (carrot oil) preparation was equilibrated to the biologic equivalence of beta carotene, since the amount of alpha carotene present was appreciable.

Following the depletion period, the two sources of carotene were fed in successive twenty-one day feeding periods at daily levels of 130, 200, 300, and 200 mg. of carotene, respectively. No differences in efficiency of utilization of the two sources of carotene could be detected. At the point of depletion both cows produced butterfats of about 12 Sherman-Munsell units per gram.

Daily intakes of 130 mg. of carotene from either source raised the butterfat unitage to 19. Two hundred milligram intakes caused the potency of the butterfat to rise to about 33 units per gram and the highest potency (36 to 37 mg. per gram) was reached when the carotene intake was 300 mg. daily, regardless of source. The authors conclude that "isolated carotene" and the carotene of alfalfa hay are equally available and equally effective as sources of vitamin A for dairy cows.

It is unfortunate that the authors have expressed potencies of feeds and butterfat in terms of the outmoded Sherman-Munsell units. In their most recent paper, they refer to carotene intakes in terms of milligrams of carotene but express the potencies of the resulting butterfats in terms of Sherman-Munsell units. According to Daniel and Munsell (*U. S. D. A. Misc. Publ. no.* **275,** *13* (*1937*)) one Sherman-Munsell unit is approximately equal to 1.4 I. U. It should be recognized that this is an average figure and will vary from laboratory to laboratory and from season to season even in the same laboratory.

However, if this factor is used in obtaining an approximate idea of the I. U. or U. S. P. equivalents, it is found that daily intakes of 770,000 I. U. (550,000 Sherman-Munsell units) in the form of alfalfa hay are required to produce a vitamin A-rich butter containing 42 or more I.U. per gram, equivalent to 30 or more Sherman-Munsell units per gram. Also, daily intakes of vitamin A in the form of fish liver oils approximated 280,000 I.U. (equivalent to 200,000 Sherman-Munsell units) to produce a butter of maximum vitamin A potency.

These findings furnish additional evidence to explain the great variability in the vitamin A content of butters produced in the various sections of the country and at different seasons of the year. Unless dairy cattle can receive adequate amounts of carotene in green feeds or properly dehydrated carotene-containing forage, it is to be expected that market butter will continue to be variable as a source of vitamin A.

THE NUTRITIONAL SITUATION IN INTERNMENT CAMPS IN FRANCE

In 1941 and early in 1942 a Commission on Hygiene was appointed by the Coordinating Committee for Relief in the Camps at Nîmes, France. An abstract of their report has been published (Zimmer, Weill, and Dubois, *New Engl. J. Med.* **230,** *303* (*1944*)), and describes the condition of more than 10,000 men, women, and adolescents. The picture is a tragic one, now all too familiar. The investigators apply the term "disease of starvation" to the syndrome which, like an epidemic, spread to all the barracks, penetrated into all the divisions, and struck all the camps.

The report necessarily had to be based on rather general physical examinations and without the benefit of laboratory studies other than urinalysis, red cell counts, and hemoglobin determinations. In many instances, however, the changes were so striking that the more exacting methods of study recently elaborated were not required to discover the presence of malnutrition. Without doubt, had such procedures been used, an even higher incidence of malnutrition would have been found than is actually recorded.

On the basis of a weight-height index calculated in relation to the physiologic coefficient of weight to height as determined by the tables of Dubois-Reymond, 63.2 per cent of the male inmates of Camp Gurs were as much as 22 per cent below physiologic weight, 24.7 per cent of the men were in a "precachectic" condition (25 to 30 per cent below physiologic weight), and 8.3 per cent were in a "cachectic" state (32 to 49 per cent below). Among the women the weight loss was even

more pronounced, there being 24.2 per cent in the cachectic class and 27.4 per cent in the precachectic. In calculating this weight-height index, the investigators had to take into consideration the errors in weight caused by edema and in height caused by scoliosis due to "the osteopathy of starvation."

The appearance of these individuals presented a tragic picture of muscular hypotony of such a degree that some dropped things they tried to hold in their hands, others collapsed, and still others were unable to make even the slightest muscular effort. Some of the internees were obliged to creep on all fours to get back to their beds, others after a few seconds or minutes on their feet complained of pricking pains in the limbs and of trembling, sometimes accompanied by profuse sweating. The appearance of some of these people is described as one of veritable anatomic dissection. It is of interest that in the considerably emaciated, hernia was almost always present.

The skin of many of the inmates was dry and scaly, their complexion ash-gray or subicteric. In many instances the general features gave a corpselike appearance. Edema was present in approximately 50 per cent. In some of the men ascites was also found. Edema was observed particularly at the top of the feet, along the inner side of the ankles, in the region under the chin and that over the cheekbones, and in the eyelids. Pain, developing after slight effort, was complained of in a number of instances as well as paresthesias; and ataxia, positive Romberg's sign, and exaggerated reflexes were described. As might be expected, the mind was not left free and in many instances the dull and apathetic gaze of the people revealed a state which often went on to disorientation and other psychic states.

In some cases the pulse rate was abnormally rapid, in others it was slow. In a few instances irregularity of the pulse was found. Anemia was present in every instance. In none of the specimens examined did the red cell count reach 4 million and in the great majority it was approximately 3 million. In barely 5 per cent of the cases was the hemoglobin above 70 per cent. In most instances it ranged about 60 per cent. It is claimed that in as many as 43 per cent of the cases, the anemia was hyperchromic.

A segmental distribution of petechiae on the back of the arms and forearms and bloody suffusions of the gums suggested the presence of scurvy in some of the subjects. As already mentioned scoliosis occurred in a large proportion of cases. Caries of the teeth was often present and in a number of cases loss of fingernails was implied. There were two instances of xerophthalmia. Night blindness was found in a number of instances.

Some complicating disorder such as tuberculosis and cardiac disease was often present. Angiospasm of the extremities of fingers and feet was frequently observed. While there were many instances of goiter, hyperthyroidism was reported as rare. In young girls puberty seemed to be retarded and cessation of menstruation was found in many of the women. It is noteworthy that no instances of diabetic coma were found.

The investigators state that a fair estimate of the caloric value of the daily fare is 950 calories per person, a figure very much below that cited for conditions in Germany and in France during World War I. The diet was particularly poor in protein of animal origin, the figure given being 15 g. per day. The daily supply of fat was not more than 8 to 10 g. per day. Needless to say, the conditions as to the freshness of food, its conservation, preparation, and variety were extremely poor. This diet was 40 to 50 per cent inferior to the diet provided the civilian population of Marseille'.

These observations do not redound to the credit of those in charge of the unoccupied zone of France in 1941 and 1942 in regard to the treatment of the many Spanish and Italian internees who were held by these

authorities. The data presented should be compared with those for the population group in an industrial suburb of Madrid, reviewed some months ago (*Nutrition Reviews* **1**, *231* (*1943*)) and in Japanese internment camps (*Ibid.* **1**, *97* (*1943*); **2**, *193* (*1944*)).

NUTRITION AND ATABRINE TOLERANCE

It has become increasingly evident in recent years that there is an interrelationship between the sciences of pharmacology and nutrition. The toxicity of many drugs is profoundly influenced by the nutritive state of the animals used for test and by the character of the diet they receive. A diet which appears entirely satisfactory for an animal leading an uneventful life may prove inadequate when the animal is called upon to resist a severe pharmacologic insult. If a drug is to be administered therapeutically or prophylactically over long periods of time, dietary considerations are likely to be especially important. Pertinent at the present time are two studies of the influence of diet on the toxicity of the antimalarial, atabrine (Hegsted, McKibbin, and Stare, *J. Nutrition* **27**, *141* (*1944*); Scudi, Jelinek, and Kuna, *J. Pharmacol. Exp. Therap.* **80**, *144* (*1944*); Scudi and Hamlin, *Ibid.* **80**, *150* (*1944*)).

It was shown by Davis and Whipple (*Arch. Int. Med.* **23**, *612* (*1919*)) that fasting augments the liver damage due to chloroform. It is known also that atabrine may produce liver necrosis (Martin, Cominole, and Clark, *J. Pharmacol. Exp. Therap.* **65**, *156* (*1939*)). Consideration of these facts led Scudi and co-workers to test the effect of inanition on the toxicity of large single doses of atabrine. Albino rats, weighing between 150 and 250 g. and maintained on a stock diet were given 450 mg. of atabrine per kilogram of body weight (50 per cent of the L.D. 50). For one group of animals there was no prior fasting, one group fasted overnight and one group fasted for thirty-six hours before the administration of the drug. There were no deaths in the first group while the mortality rates were 22 per cent and 48 per cent, respectively, for those fasting overnight and thirty-six hours. There was severe liver necrosis in all of the rats given the atabrine, and plasma fibrinogen concentrations were appreciably increased. Fibrinogen values were found by the authors to parallel the toxic effects of atabrine upon the liver. This is not as startling as it appears at first glance, since Foster and Whipple (*Am. J. Physiol.* **58**, *407* (*1922*)) have shown that destruction of liver tissue may cause increased fibrinogen values and that low values are obtained only when the loss of liver tissue has become so great that the organ can no longer meet the needs of the body for fibrinogen production.

Scudi and Hamlin investigated the influence of the protein and fat levels of the diet on the toxicity of atabrine for rats. One group of albino rats was placed on a 6 per cent protein diet and another group on a diet containing 30 per cent of protein. The fat content of each of these two diets was 11 per cent. After seven weeks the weights of the animals in the low-protein group were 100 to 160 g. and of those in the high-protein group 200 to 300 g. At this point each group of rats was subdivided into a group receiving 2 per cent of fat and another receiving 47 per cent of fat. The protein levels of the diets were altered slightly, from 6 per cent to 4 per cent for those which had been receiving the low-protein diet, and from 30 per cent to 45 per cent for those which had been receiving the high-protein diet. After a two to three week period of equilibration on the new diets, rats from each group were given daily doses of atabrine at a level of 45 mg. per kilogram of body weight. All of these animals except the ones on the

high-protein, low-fat diet showed changes due to the toxic effects of the atabrine. They lost weight and presented evidences of diarrhea, the pelage became disheveled and the whiskers encrusted with porphyrin-like materials (a sign of dehydration). Activity was depressed and plasma fibrinogen values were increased. The authors conclude that rats on a high-protein, low-fat diet resist the toxic effects of atabrine to a greater degree than rats given a low-protein diet or a diet high in both protein and fat.

Scudi and Hamlin extended their study of the effect of protein nutrition on atabrine toxicity to include dogs. Preliminary experiments showed that inanition resulted from the daily administration of atabrine at levels of 25 or 50 mg. per kilogram of body weight. Since inanition would augment the toxicity of the drug and thus make difficult the interpretation of the results obtained, a different experimental approach was adopted. Plasma proteins were first depleted by a low-protein diet and then, with continuation of this diet, 10 mg. of atabrine per kilogram of body weight were given daily. Normal dogs on a stock ration receiving the same dosage of the drug served as controls. Increased fibrinogen levels developed in the protein depleted dogs. Subsequent restoration of protein to the diet caused the fibrinogen levels to return to normal.

Hegsted, McKibbin, and Stare investigated the effects of single deficiencies (protein, riboflavin, and vitamin A) on the toxicity of atabrine as well as the effect of increasing the intake of various dietary essentials above the level of minimum requirements. Atabrine was fed to young albino rats in purified diets at levels of zero to 65 mg. per 100 g. of ration. Since the daily food consumption was approximately 10 per cent of the body weight, this corresponded to levels of zero to 65 mg. per kilogram of body weight. In adequate diets, with the intake of water soluble vitamins near or slightly below the optimum levels, 25 mg. per cent or less of atabrine over six months periods caused no growth retardation or other abnormalities. At dietary levels of 40 and 65 mg. per cent for three months, the animals developed an unkempt appearance, there was discoloration of the fur and the growth rate was depressed by 20 to 35 per cent. The addition of various vitamins, yeast or protein to the already adequate diet did not prevent these changes. Histologic examination was made of the tissues of rats which had received 25 and 40 mg. per cent of atabrine for six months. No necrotic changes were detected. This is in general agreement with the results of Wright and Lillie (*Pub. Health Reports* **58,** *1242 (1943)*), who fed 30 mg. of atabrine per kilogram of body weight daily for fifty days to rats receiving a diet of Purina dog chow. These authors found histopathologic changes but no necrosis in various organs and noted that the lesions were on the average slightly diminished in intensity by the inclusion of whole dried liver or whole dried kidney in the diet. In the studies of single deficiencies, Hegsted *et al.* found that the slow rate of growth obtained on suboptimal levels of riboflavin or protein was further decreased by the addition of 40 mg. per cent of atabrine to the diet. With diets suboptimal in vitamin A, however, this effect was not observed. From studies on the levels of atabrine needed to reduce the growth rate by 30 per cent, the authors conclude that the chick is from three to four times as tolerant of atabrine as is the rat.

Hegsted, McKibbin, and Stare (*J. Nutrition* **27,** *149 (1944)*) also made the interesting observation that atabrine protects rats against the kidney hemorrhages caused by choline deficiency. Diets containing 10 per cent of casein and 6 per cent of casein + 30 per cent of alcohol extracted peanut meal were used and in one experiment the rats were pair-fed. There was a high incidence of kidney hemorrhages in the control animals not given the drug. Atabrine at 40 mg. per cent in the 10 per cent casein diet afforded

the rats nearly complete protection against this damage. With the peanut meal ration, 65 mg. per cent of atabrine was almost completely protective while 40 mg. per cent was somewhat less. The mechanism by which atabrine protects the kidneys against hemorrhagic degeneration is not clear. Limitation of growth is known to decrease the severity of kidney damage. In the paired feeding experiment, the control animals gained in weight a little more rapidly than those receiving the drug, but the difference does not seem to be sufficient to account for the protective action of the drug. The atabrine molecule contains two ethyl groups and one methoxyl group but as Hegsted *et al.* point out, there is no evidence that transethylations occur in the body nor that methoxyl groups are available for transmethylations. Furthermore, atabrine appears to be somewhat too potent a protective agent for this action to be explained on the basis of transmethylation. The authors state that they are investigating the possibility that an effect on the choline esterase system may be involved. It is interesting that atabrine gave no lipotropic effect at the levels fed. Griffith (*J. Nutrition* **22,** *239 (1941)*) has pointed out that with dietary casein levels of 18 to 24 per cent, hemorrhagic degeneration of the kidneys is prevented by 1 to 2 mg. of choline chloride per day, while 4 to 6 mg. are necessary to prevent the deposition of liver lipids. It appears, therefore, that an investigation of the possible lipotropic effect of higher levels of atabrine might throw considerable light on the nature of the protective mechanism. Whatever this mechanism may be, these investigations and those of Scudi and co-workers offer a further clear indication of the interdependence of the nutrition of animals and the action of drugs in the body.

VITAMIN BALANCE STUDIES ON A MILK DIET

One of the critical steps in the study of nutrition at the present time is the determination of the human utilization of nutrients in food. Milk warrants a prominent place in such investigations since it plays a major role in infant nutrition, the normal adult diet, and the therapeutic diet which is often restricted either wholly or in large part to milk.

Gardner, Peterson, and Parsons (*J. Am. Dietet. Assn.* **19,** *683 (1943)*) have investigated the biotin, pantothenic acid, and riboflavin contents of the urine and feces of 3 healthy young women when mineralized milk constituted the only food eaten for ten days, with the exception of caramel candy which was allowed ad libitum to supplement the caloric intake. One quart of milk was consumed at each meal. In addition, supplements of 50 mg. of ascorbic acid and 5 ml. of mineral mixture were given daily. The mineral mixture contained 8.5 g. of iron pyrophosphate, 0.4 g. of copper sulfate, and 0.4 g. of manganese sulfate in a pint of water. The daily intake of milk was found to provide 115 micrograms of biotin, 6.9 mg. of pantothenic acid, and 7 mg. of riboflavin. Vitamin assays were made by the yeast growth and microbiologic methods.

The resultant urinary output of biotin, pantothenic acid, and riboflavin averaged 49.5 micrograms, 6.0 mg., and 3.4 mg. respectively; the fecal output averaged 73.4 micrograms, 0.41 mg., and 0.42 mg. in the same respective order. Thus, the total biotin in the excreta was divided about equally between the urine and feces, and a small excess of total output over intake was observed in 2 of the 3 subjects. The kidney was the principal channel of excretion of riboflavin and pantothenic acid. The total output of pantothenic acid almost equaled the intake. For all 3 subjects the urinary pantothenic acid was less during the seventh to tenth day than during the fourth to sixth

day. The authors note that this probably indicates only the variation which occurs between successive collection periods. An extension of the period of study would have clarified this point.

The total output of riboflavin accounted for only about 55 per cent of that ingested. These data would suggest either considerable destruction or retention of riboflavin. While it is generally assumed that the storage of water soluble vitamins is limited, Elvehjem (*J. Am. Dietet. Assn.* **19,** *743 (1943)*) has pointed out the possibility of considerable storage since muscle tissue, constituting over 40 per cent of the body weight, may vary widely in its vitamin content depending upon the previous dietary intake. Certain other organs of the body have been found to vary considerably in vitamin content, depending upon the previous vitamin intake. It would probably have been desirable to correlate the results of the above balance study with a preliminary balance study made on the self-chosen diet or at least with a diet history covering the previous dietary intake. Such information would probably be of significance in reconciling conflicting results obtained from various laboratories.

The value of the above report will be enhanced by a series of further investigations with normal individuals. Furthermore, such investigations will be of basic importance in comparative studies made with abnormal individuals. Balance studies of this nature are of fundamental significance to the clinician using diet therapy.

FATE OF LARGE DOSES OF THIAMIN AND RIBOFLAVIN

The fate of the B-complex vitamins when large doses are given to experimental animals is incompletely understood. Interest in this problem is prompted by a number of considerations. If the vitamins are merely excreted or not absorbed when large amounts are administered, then there may be little reason to give generous doses to deficient patients or animals. Yet many clinicians have reported better therapeutic responses with large than with small or moderate amounts. If the vitamins are retained by the body, it is conceivable that stores of sufficient magnitude may be built up to tide the animal over long periods of deficient intake or that toxic tissue concentrations may be obtained. There is evidence, however, that some of the B-vitamins, like thiamin, cannot be stored in quantities great enough to protect against sustained dietary inadequacies, and no generally accepted evidence has been published to show that the B-vitamins in large amounts are toxic. Finally, if the nutrients are absorbed in great quantities, it is possible that they may be destroyed within the tissues of the body. Partial answers to some of these possibilities have been given for thiamin and riboflavin in experiments done on rats.

Leong (*Biochem. J.* **31,** *367, 373 (1937)*) found that rats excreted insignificant amounts of thiamin in the feces, apart from the output due to bacterial synthesis, when the daily ingestion was less than 150 micrograms. Greater levels of intake resulted in incomplete absorption. Maximum storage of the vitamin was obtained when the intake was 90 micrograms per day; increases above this level did not result in any appreciable accumulation of tissue reserves. Subcutaneous injection of 750 micrograms of vitamin B_1 was followed by urinary excretion of 75 per cent of the dose. Leong, however, used the bradycardia method of detecting deficiency. His results were qualitative rather than quantitative and cannot be compared in accuracy with more recent studies in which chemical determinations of thiamin have been possible.

Light, Schultz, Atkin, and Cracas (*J. Nutrition* **16,** *333 (1938)*) discovered that rats reach an excretion equilibrium when given

15 to 515 micrograms of thiamin per day. Twenty-five to 35 per cent of the ingested vitamin was excreted via the urine, 20 to 30 per cent through the feces, and the remainder was unaccounted for. The animals were fed a vitamin-supplemented purified diet and thiamin in the urine and feces was determined by chemical analysis. It is interesting to note that animals with a history of low vitamin B_1 intake showed a time lag before the excretion equilibrium was reached. If, however, the excretion equilibrium had been attained at intake levels between 50 and 65 micrograms, then further additions of thiamin were promptly excreted in the percentages indicated above. After the subcutaneous injection of 200 to 500 micrograms of thiamin, 75 to 85 per cent of the dose could be recovered in the urine. In an attempt to find the 35 to 55 per cent of orally administered thiamin which could not be recovered from the excreta, the same authors analyzed the tissues of their animals for the vitamin (*J. Nutrition* **17,** *143 (1939)*). At feeding levels between 10 and 65 micrograms per day, the tissue concentration was directly related to the intake level. With doses greater than 65 micrograms, however, the tissue concentrations were not further increased. A large percentage of the ingested vitamin, therefore, could not be accounted for.

Sure and Ford (*J. Nutrition* **26,** *659 (1943)*) have extended these observations and studied riboflavin utilization as well. Their experiments were conducted on 24 male albino rats, 36 days of age. The animals were fed ad libitum a ration of the following percentage composition: casein 18; agar-agar 2; butterfat 10; dextrose 66; and a salt mixture 4. Daily supplements of 20 micrograms of pyridoxine, 6 micrograms of choline chloride, and 200 micrograms of calcium pantothenate were also given. Thiamin and riboflavin were fed in daily amounts of 5, 10, 20, 50, 100, and 1000 micrograms. Animals were divided into groups of 4, 2 of which received the same dose of both vitamins, one was given thiamin only, and the fourth riboflavin only. Fecal specimens were collected and preserved under petroleum ether in order to minimize bacterial synthesis. Three of the 6 groups were studied for twenty-six days; the other 3 for thirteen days. In all the calculations, allowances were made for the thiamin excreted on a thiamin deficient ration and for the riboflavin excreted on a riboflavin deficient diet. The fecal excretions for thiamin, as the per cent of the total intake, began to rise with the 20 microgram dose and reached a level of 27.8 per cent with the 1000 microgram allowance. The per cent of the thiamin excreted in urine, however, did not begin to rise until the 100 microgram dose; it became as great as 34.8 per cent at the 1000 microgram level. The total excretion, in both urine and feces, varied from 8 per cent when 10 micrograms per day were given to 64.9 per cent on the highest dose. With the larger doses, therefore, there was less efficient absorption and greater urinary loss.

For riboflavin, the results were in distinct contrast. Only the experiments with the three larger doses were considered valid because it was felt that data obtained at the lower feeding levels were made inaccurate because of the factor of bacterial synthesis in feces. The per cent absorbed and the per cent lost in urine remained relatively constant with the increasing doses. Approximately 26 per cent was excreted in the urine and feces with the 50, 100, and 1000 microgram allowances.

With both vitamins, however, in spite of the decreased utilization of thiamin at the higher feeding levels, large amounts were unaccounted for. They were either retained by the tissues or destroyed during metabolism. In order to measure the storage, 12 additional male rats were fed the purified diet for thirty days; half the animals received 100 micrograms each of thiamin and riboflavin per day while the other 6 were given ten times that amount. Their tissues were

then analyzed. The thiamin and riboflavin contents were not appreciably greater on the 1000 microgram dose than on the 100 microgram allotment. The experiment with the larger dose was then repeated and the vitamins in the entire bodies of the rats were determined. After 30,000 micrograms of both thiamin and riboflavin, the average content per animal was only 125 micrograms of thiamin and 783 micrograms of riboflavin. It was apparent, therefore, that the rat had only a limited capacity for storing these two vitamins. The fate of the missing fraction of the vitamin is unknown but the authors demonstrated that *in vitro* incubation of thiamin and riboflavin for twenty-four to forty-eight hours at 37°C with liver, lung, heart, stomach, and intestines led to considerable destruction of both vitamins (12 to 28 per cent destroyed within forty-eight hours).

Evaluation of these interesting results must be made with the realization that large technical errors may exist in some of the determinations, particularly those of riboflavin excretion in feces. However, if tissues do destroy large amounts of thiamin and riboflavin, the metabolism involved may have practical as well as theoretical significance. Those deficient human subjects, for instance, who require large doses of the vitamins before maximum therapeutic benefit is derived, may metabolize them at an unusually rapid rate.

CORN GERM, A VALUABLE PROTEIN FOOD

The war has stimulated the search for new food materials and for supplements to improve existing foodstuffs. This is in part the result of real or threatened war shortages, but perhaps also in part the result of an increased awareness that enormous numbers of people throughout the world are handicapped by inadequate nutrition. The temporary war needs of the better fed communities are similar to the permanent needs in habitually underfed parts of the world. Food discoveries of wartime may thus become of permanent benefit to postwar nutrition.

There is a particularly pressing need for increased and cheaper sources of high quality protein. Protein of indisputably high quality, protein of animal origin, is too costly for great sections of the world population. It is therefore gratifying to learn from several recent reports that corn germ, which constitutes about 7 per cent of the corn kernel, contains 20 per cent protein of surprisingly high quality.

Block and Bolling (*Arch. Biochem.* **3,** *217 (1943)*; *J. Am. Dietet. Assn.* **20,** *69 (1944)*) have found that the amino acid composition of corn germ protein is comparable to that of milk protein. This is in contrast to most of the other plant proteins investigated to date which are of only fair quality for nutrition because of inadequate amounts of certain essential amino acids, notably lysine and valine.

The final test of the "quality" of protein is its efficiency in nourishing animals, its so-called biologic value. Mitchell and Beadles (*Science* **99,** *129 (1944)*) have now tested the digestibility and biologic value of corn germ protein, and compared it in these respects with meat and soybean proteins. They used a sensitive method which has been extensively employed in a variety of investigations by Mitchell and co-workers. The method consists in feeding the material to be tested for about a week to young growing rats, during which time the fecal and urinary nitrogen are measured separately. The "true digestibility" is the per cent of fed nitrogen which is absorbed, and the biologic value is the per cent of the absorbed nitrogen which is retained by the animal after making in each case due allowance for fecal and urinary nitrogen excretion on a nitrogen-free diet.

One criticism of this type of method is that

the test material is fed for only a short period. It seems possible that a suboptimal concentration of a particular amino acid in the protein, which would ultimately prove to be a handicap to the animal, might be without consequence for the nitrogen balance during a short test period. The method has, however, proved to be highly useful, and many valuable data have been obtained through its use.

In this instance, using a group of 10 rats, it was found that the protein of defatted corn germ has a true digestibility of 85 per cent and a biologic value of 78 per cent. For beef round and autoclaved soybean, respectively, the coefficients of true digestibility were 100 and 84 per cent and the biologic values, 76 and 67 per cent. Thus, although only 85 per cent of the corn germ protein was digested, the digested fraction was equal in quality to the protein of beef. Corn germ and autoclaved soybean proved to be equally well digested, but corn germ protein was of distinctly better quality.

"The average biological value of 78 obtained for this sample of corn germ may be compared with values of 50 to 65 obtained for the cereal grains, 51 to 60 for a series of nuts widely used in the American diet, 72 for the cashew nut, 94 for whole egg, 90 for raw whole milk, and 62 to 77 for various cuts of meat and edible animal organs." Thus corn germ is outstanding among vegetable products and is exceeded in quality by only a few animal proteins. Wheat germ has an amino acid composition similar to corn germ, and is presumably of similar high biologic value.

The above biologic values were all obtained by Mitchell and co-workers by comparable methods. This is important, since a variety of methods and modifications exist for the measurement of biologic value, a situation which has resulted in considerable divergence in the absolute biologic value obtained for any particular foodstuff. It is therefore difficult to compare data from different laboratories.

Mitchell and Beadles also found 26 micrograms of thiamin per gram of corn germ, which compares favorably with wheat germ. The high thiamin content and protein quality indicate that corn germ would be an excellent food for man. This conclusion is perhaps surprising in view of the rather widespread prejudice against corn itself as human food. The prevalence of pellagra in regions where corn meal (germ free) has largely replaced wheat as the chief cereal, and the low biologic value of the purified corn protein zein, which is of course but one of the many corn proteins, may account for this prejudice.

Mitchell and Beadles estimate the potential American production of corn germ at one-half million tons per year. This amounts to about 7 pounds per capita. Although this 7 pounds would contain the individual thiamin requirement for two or three months, it would represent the protein requirement for only about ten days. Therefore, although this is a definite step in the right direction, the search must continue for cheap, plentiful sources of high quality protein.

FAT IN THE DIET OF THE DAIRY COW

For some time dairymen and manufacturers of dairy feeds have been faced with the question of how much fat there should be in the grain mixtures of milking cows. Great interest has arisen in this question during the war period in which, with an unprecedented military, industrial, and domestic demand for fats and oils, new importance has been given to their extraction from products, the extraction residues of which are used in dairy feeds. At the present time dairy feeds contain approximately 2.00 to 2.75 per cent fat as compared to 3.50 to 4.50 per cent of fat in prewar years. The

problem is that of determining how much fat must be left in the extraction residue to make it acceptable to the dairyman for fulfilling the requirements of milk production which is also vital to the war effort.

Some of the fundamental aspects of this question are not new, the early work of Jordan having shown that carbohydrate could be used for butterfat production by the cow. On the basis of this finding, it was thought for many years that fat was of no particular consequence in a dairy ration. However, Maynard and McCay (*Cornell Univ. Agr. Exp. Sta. Bull.* **543** (*1932*)) and Maynard, McCay, Williams, and Madsen (*Ibid.* **593** (*1934*)) showed that the fat in the diet of the dairy cow played a definite role in the production of milk and butterfat. Further work by Maynard and associates was summarized in a report in 1940 (*Proc. Am. Soc. An. Prod. p. 340* (*1940*)). In this report are given the results of nine different feeding trials conducted between 1928 and 1940 and involving 105 cows fed on various levels of fat. All of the trials, except one, resulted in a higher average milk production when a higher fat level was fed, and the average figures were also higher for butterfat and fat-corrected milk. The fat levels in the concentrate portion of the feed ranged from 0.7 to 7.5 per cent. These results would seem to be highly indicative if not conclusive evidence in favor of high-fat rations, but a final opinion on this question must be reserved in the light of the findings of a number of other workers. The grouped observations and conclusions of these workers have not agreed in all respects with the Cornell workers but may be summarized as follows: (1) The character of butterfat may be influenced by the feeding of different fats and oils. (2) The feeding of various oils has sometimes resulted in an increased butterfat test and increased milk production, but in some instances, butterfat tests and even the milk yields have been decreased. (3) Different oils may exert a different effect on butterfat production and on milk production.

The work of Monroe and Krauss (*J. Dairy Sci.* **23,** *558* (*1940*)) is as recent and perhaps as extensive as that of any other workers. They have concluded their most recent report as follows: "Under the conditions of these trials no significant differences were observed in the production of milk, butter fat, or 4 per cent (F. C. M.) milk or in the general health of milking cows from the feeding of practical grain mixtures ranging in average fat percentage from 4.89 to 2.69." On first thought it might seem that this is a practical and final answer to a highly important economic and physiologic problem. It is, however, difficult to reconcile these results with those obtained by Maynard and associates, unless one accepts as the whole explanation the fact that the fat levels compared by Monroe and Krauss are lower than those employed by Maynard. It is debatable whether this fact elucidates the results. Rather it is felt that further work dealing with the fundamental aspects of this problem would be highly desirable. In this connection a report by Lucas and Loosli (*J. Animal Sci.* **3,** *3* (*1944*)) is of interest. These workers have reported an investigation involving digestion trials with cows fed different levels of fat from different sources, testing whether a more efficient absorption of nutrients had occurred on high-fat as compared with low-fat rations. Although some differences were observed, the results in general with respect to the production of milk fat and fat-corrected milk bore no consistent relation to the actual intake of ether extractable material and total digestible nutrients.

It would appear, therefore, that the ultimate solution of this problem should depend on a fundamental approach involving more than feeding trials or digestion studies. Maynard's early results with respect to the composition of milk fat indicate that "more

physiological processes are involved where the food source of fat is carbohydrate rather than fat itself." Therefore, the need for an investigation of fundamental character would seem to be indicated.

The economic aspects of this problem are large. It has been estimated that there would be, on the average, 23,300,000 milk cows in production during 1944 in the United States, producing 4639 pounds of milk per cow in order to meet the 1944 production goal of 121 billion pounds of milk. Over 18 million tons of grain mixture will be consumed by these cows. A sizable fraction of these 18 million tons of feed consists of (1) oil meals, representing oil extraction residues, and (2) other feeds which, although perhaps not particularly rich in fat, are potential sources of fat for industrial, specialized, and even human diet purposes if not required in the diet of the cow. It can easily be seen that a large amount of fat and oil can be obtained by a small percentage reduction in the fat content of dairy feeds. If present practices involving less fat in dairy feeds do not lower butterfat and milk production, the result is a net gain to the nation's fat and food supply.

SUPPLEMENTATION OF THE DIET IN GREAT BRITAIN

The method of therapeutic trial under adequately controlled conditions has furnished valuable information in the investigation and diagnosis of deficiency disease in individual patients. The application of this method in estimating the prevalence and type of nutritional inadequacy in population groups can be expected to find an increasing field of usefulness, especially in an attempt to confirm evaluations of the nutritional status obtained by survey methods. Just as in investigations of individuals it is necessary to control conditions accompanying the response to therapy to avoid *post hoc, propter hoc* errors, so in dealing with groups a concomitant study of a comparable group not receiving treatment, together with statistical analyses of the differences found, is necessary.

Davidson and Donaldson (*Brit. Med. J.* **1,** *76* (*1944*)) report such a study on the effect of small supplements of iron and ascorbic acid on the hemoglobin levels of Edinburgh municipal schoolchildren, between the ages of 5 and 12 years. Clinical anemia had previously been found in approximately 40 per cent of these children (Davidson, Donaldson, Lindsay, and McSorley, *Brit. Med. J.* **2,** *95* (*1943*)), using a level of 80 per cent of normal as the criterion. The British standard of 100 per cent corresponds to 14.8 g. of hemoglobin per 100 ml. according to the recent independent investigations by Macfarlane and co-workers (*Brit. Med. J.* **1,** *248* (*1944*)). In school I, 324 control and experimental subjects were divided into groups according to whether they took the midday meal at home, took the school lunch and paid for it, or were given free school lunches. The treated groups received 0.2 g. of ferrous sulfate a day, five days a week, for a period of three months. No significant changes in the mean hemoglobin level occurred in any of the control groups, but they were significantly higher in all of the experimental groups. The change was small in the children eating their noonday meal at home, who had an initial mean level of 85 per cent, but hemoglobin values rose from an initial level of 80 to a mean of 86 per cent at the end of three months in those children eating the school lunch. Of especial interest was the change in subjects whose hemoglobin levels were less than 80 per cent at the initial examination. Of 59 such children in the control group, 52 per cent remained below this level at the second examination, whereas

of 71 receiving iron supplements, only 34 per cent remained below the standard.

Experiments in school II on 170 subjects indicated no effect on the hemoglobin levels with small supplements of ascorbic acid. One group of 57 served as controls, a group of 56 received 25 mg. of ascorbic acid daily for five days a week, and a third group of 57 received the same ascorbic acid supplement plus 0.2 g. of ferrous sulfate five days a week. At the end of three months no rise had occurred in the mean levels of the control group or the group receiving only ascorbic acid, while the level in the group receiving iron was significantly higher than that of the control group. Again, the change in those subjects whose initial levels were below 80 per cent of "normal" was most informative. Of 26 such children in the control group, 58 per cent were still below 80 per cent hemoglobin after three months; of 19 receiving ascorbic acid alone, 68 per cent remained below 80 per cent hemoglobin on the second examination; of 19 receiving iron and ascorbic acid, only 21 per cent fell below this level on the second examination.

In school III only children with initial hemoglobin figures below 80 per cent were studied, with 27 subjects in the control group and an equal number receiving 25 mg. of ascorbic acid and 0.4 g. of ferrous sulfate five times a week. The initial mean levels of both control and experimental groups were 78 per cent; after three months the mean level for the control group was 81 per cent, for the supplemented group 87 per cent. At the end of six months the mean level for the control group had come up to 88 per cent, and that of the supplemented group to 94 per cent. These levels were significantly higher for the treated children at both the second and third examinations.

The authors believe that these findings indicate that the hypochromic anemia which has been found to be prevalent in certain strata and groups of the population of Great Britain can be definitely attributed to an insufficiency of iron in the diet. They note that these observations are essentially from the viewpoint of prophylaxis and that in treatment of individual cases of anemia much larger doses of iron should be used. With numerous reports indicating that such anemias are the most definite physical change resulting from war restrictions in Great Britain (*Nutrition Reviews* **1,** *85 (1943)*), the demonstration of their main etiologic factor together with a simple method of control is timely and valuable.

A somewhat different type of study, indicating that supplementation of the English diet with a multivitamin preparation had no effect on the growth, health, and physical fitness of schoolchildren and adults, is reported in summary form by Bransby and co-workers (*Brit. Med. J.* **1,** *77 (1944)*). One thousand two hundred and forty-two schoolchildren between 5 and 14 years of age were studied in three different localities, being divided at random into two equal groups according to school, age, and sex. One group received every school day a capsule containing 4000 I.U. of vitamin A, 1 mg. of thiamin, 2 mg. of riboflavin, 50 mg. of ascorbic acid, 20 mg. of nicotinamide, and 600 I.U. of vitamin D. The other group received a placebo capsule of arachis oil. The test was carried out from November 1941 to August 1942, with examination, including dental examination, of the children before, during, and after the period of supplementation. Records were kept of the nature and duration of all illnesses. Muscular strength was measured in some groups by a dynamometer; in one group a test of muscular endurance by hanging on a bar was done. The findings were similar in all localities. The comparison of the experimental and control groups with respect to rate of growth, nutritional status, muscular strength, condition of teeth and gums, and absence from school on account of illness showed that no statistically significant effect had been obtained from the vitamins.

In two factory tests on 214 adult men en-

gaged in strenuous and exhausting labor in zinc smelting, a similar division into vitamin-supplemented and control groups was made. The vitamin capsules had no significant effect on weight, hemoglobin level, blood pressure, absence due to illness, or average daily output of material. Conditions in the factory tests were such that only relatively large differences in output of material would have been evident.

In the interpretation of a study of this sort the level of supplementation, the length of time it is given, and the criteria used to estimate its effect are of great importance. The level of supplementation used was roughly in the neighborhood of the average daily requirement and not in the range of therapeutic dosage required in the treatment of specific deficiency disease. Although the significance of mild and chronic vitamin deficiencies in man are subject to controversy (*Nutrition Reviews* **1,** *118* (*1943*)), it is pertinent to observe that both level and duration of vitamin administration were insufficient to permit correction of changes of this type. The criteria used were growth, general health, and physical fitness, all of which are dependent on other factors in addition to the nutritional state. Nevertheless, the study indicates that no immediate improvement was accomplished by multivitamin preparations at the dosage level used.

ASCORBIC ACID IN CHICK NUTRITION

Briggs, Luckey, Elvehjem, and Hart (*Proc. Soc. Exp. Biol. Med.* **55,** *130* (*1944*)) have reported that ascorbic acid has growth-promoting activity for chicks when added to certain highly purified rations. The mechanism of the effect is unknown but one of the possible explanations suggests that ascorbic acid cannot be synthesized by the chick on a highly purified ration fast enough to permit maximum growth.

Day-old white Leghorn chicks in groups of 6 were placed in electrically heated cages with raised screen bottoms and fed ad libitum a basal diet consisting of dextrin, casein, gelatin, soybean oil, and salts. To each 100 g. were added 20 micrograms of biotin, 0.1 g. inositol, 0.3 mg. thiamin, 0.4 mg. pyridoxine, 0.6 mg. riboflavin, 1.5 mg. pantothenic acid, 150 mg. choline, 10 mg. niacin, 500 micrograms of 2-methyl-1,4-naphthoquinone, and 300 micrograms of alpha-tocopherol. Three drops of a vitamin A and D concentrate were also given per week to each chick. This ration is presumably lacking in vitamins B_{10}, B_{11}, and possibly in "folic acid"; it supported only poor growth and feathering and produced anemia in the chicks. The missing nutrients appeared to be replaced by the addition of 2 per cent solubilized liver to the ration. Briggs and associates made the following pertinent observations:

(1) When ascorbic acid and para-aminobenzoic acid were fed together at high levels (20 to 100 mg. and 0.5 to 10 mg. respectively), the growth obtained approximated that shown when solubilized liver was added to the ration. Neither ascorbic acid nor low levels of para-aminobenzoic acid promoted growth when fed alone to chicks on the basal ration. In previous studies (Briggs and co-workers, *Proc. Soc. Exp. Biol. Med.* **52,** *7* (*1943*)) evidence was presented to show that para-aminobenzoic acid is not a specific growth factor for chicks, but acts indirectly by stimulating the production of unknown vitamins through intestinal synthesis.

(2) Even when chicks were fed the diet including 2 per cent solubilized liver, addition of 100 mg. of ascorbic acid or of 500 micrograms of para-aminobenzoic acid stimulated small but consistent gain in weight, although the two supplements together had no additive effect.

(3) Arabinose, fed at a level of 1 per cent, promoted growth to the same degree as did

ascorbic acid. Growth of chicks on a practical farm ration, low in or free of ascorbic acid, was not helped by the addition of this vitamin. The authors point out, however, that the practical ration contains arabinose and other carbohydrates which may have the same effect on growth as does ascorbic acid.

(4) Determinations of the ascorbic acid content of livers on chicks which had received 100 mg. ascorbic acid per 100 g. of ration showed that at thirteen days the concentration was almost twice that of controls, but at four weeks the difference was much less marked.

These results are interesting since they show a nutritional effect of a vitamin known to be synthesized by the chick. The mechanism through which ascorbic acid exerts its effect is unknown. The suggestion was made that it might alter conditions within the intestinal tract so as to cause more effective utilization of essential nutrients or greater synthesis by intestinal bacteria of "unknown vitamins." Also, as stated in the first paragraph, it is conceivable that the rate of ascorbic acid synthesis by chicks is not rapid enough to permit maximum growth. Some support is given to this possibility by the observation of Bell, Satterfield, and Cook (*Proc. Soc. Exp. Biol. Med.* **48,** *473 (1941)*) that 4 hens fed a diet deficient in ascorbic acid developed a leg paralysis and other evidences of deficiency while they were "under the demands of heavy egg production"; the signs disappeared after the subcutaneous injection of vitamin C. Until the action of ascorbic acid is understood, however, it seems wisest, as Briggs states, to regard the effect of the vitamin as one of growth stimulation rather than as evidence that it is a growth factor for chicks.

METABOLISM OF BONE SALTS IN RESISTANT RICKETS

Rickets resistant to treatment with ordinary doses of vitamin D is frequently associated with renal disease. However, numerous cases of resistant rickets are encountered which are not thus complicated, and a clear understanding of their nature is wanting.

Such chemical balance studies of the bone salt metabolism as have been carried out have shown changes in calcium and phosphorus metabolism which were not typical of ordinary infantile rickets and yet were not at all like those in primary hyperparathyroidism. An interesting contribution to this problem comes from the studies of Gunther, Cohn, Cohn, and Greenberg (*Am. J. Dis. Child.* **66,** *517 (1943)*) who had an opportunity to study the fate of radioactive phosphorus in a case of resistant rickets.

Their patient's illness had been a diagnostic problem since he was 4 months of age. At that time he refused the breast feeding and on weaning his appetite failed. Various modifications in diet were made and ultraviolet irradiation with a mercury vapor lamp as well as calcium supplements were given from the time the feeding difficulties commenced. Cod liver oil was also administered, but in spite of apparently adequate amounts of vitamin D, a severe bilateral genu varum (outward bowing of the leg) was noted at the age of 2 years. This affected the entire lower extremity, and with it was a coxa vara (curvature of the neck of the femur) and loss of abduction. Roentgenograms revealed changes which seemed typical of rickets. As his age advanced, further changes suggested a diagnosis of achondroplasia at times, although the evidence favored rickets rather than the former disease. The blood calcium was 10.4 mg. (normal) and the inorganic serum phosphorus was 3.3 mg. (below normal). In addition, from the age of 3 years small pockets of pus developed in the gums from time to time and these were often accompanied by bouts of fever. Such

attacks were repeated from time to time and led to the extraction of a number of teeth. All the teeth which were extracted were sound.

When the child was 11 years of age studies revealed that a positive calcium and phosphorus balance could be maintained only with a high intake of calcium and phosphorus. With a low intake of calcium the balances of both these substances became negative. Measurement of the fecal content revealed that the shifts in balance corresponded to changes in the amount excreted in the feces.

Radioactive phosphorus was given to the patient while he was in the postabsorptive state as well as together with food. The radioactive phosphorus content of the urine and feces, collected continually for a week after admission, was measured. The results revealed that there was practically complete absorption of the administered phosphorus in the postabsorptive state. When the phosphorus was given with food, there was a decreased absorption of administered phosphorus. It appeared that a considerably larger fraction of the administered phosphorus remained unabsorbed and was swept through the intestine when the phosphorus was administered with food than when administered while the subject was in the postabsorptive state. Nevertheless substantial quantities were absorbed in either state.

The tracer experiments with labeled phosphorus thus lend no support to the hypothesis that the absorption of phosphorus is a limiting factor in determining the healing or nonhealing of resistant rickets. The authors point out that the absorption of calcium may be the limiting factor although nothing in their experiments either confirmed or refuted this possibility. They argue, however, that since rickets is primarily a disease of phosphorus deficiency (at least in the rat), in the light of their observations the primary defect in this disease is not the absorption of the bone salts, but rather lies in a failure of the calcifying mechanism.

NUTRITIONAL STANDARDS IN TROPICAL CLIMATES

The nutritional requirements of man in hot climates have been the subject of much discussion. It is generally recognized that several factors may alter these requirements under such climatic conditions. Not only may copious sweat production lead to an extra loss of certain bodily reserves, but it has also been suggested that a hot environment leads to a more specific increase in the requirements for certain nutrients. In addition, and perhaps one of the most important factors concerning adequate nutrition, is the loss of appetite commonly experienced in individuals not adapted to such an environment. Since many questionable assumptions have also been made concerning the correct dietary in tropical climates, an evaluation of the subject by Johnson (*Gastroenterology* **1**, *832* (*1943*)) is timely and instructive.

It is an old established custom to restrict fluids during work, on the assumption that intake of water is deleterious. Johnson points out that this custom has no basis in physiology although it is admitted that the water taken should not be ice cold and should not be consumed in amounts large enough to interfere with muscular activity. In a tropical climate as much as a liter of water per hour can be lost by an active man in good condition through sweat. It is stated that experiments have demonstrated conclusively that the best performance even in men in good condition is obtained when water balance is maintained from hour to hour by frequent ingestion of water in amounts even greater than necessary to keep thirst quenched at all times. It is obvious that these optimal quantities of water may not always be accessible. The minimal requirements and the spacing of water intakes cannot be pre-

cisely defined, but the evidence at hand indicates that the Army practice is a good one; namely, to drink as much as is practical before starting the day's work and to conserve the water in the canteen until the noon and evening halts.

Another traditional viewpoint is that the specific dynamic action of protein is so great that it places a stress upon the mechanisms for dissipating heat, and therefore protein should be limited in hot climates. Johnson points out that in comparison to the heat expenditure of a man marching with a 40 pound pack, the effect of a meal rich in protein on the heat dissipating mechanism is insignificant in most instances. His laboratory experiments as well as the food habits of many laborers in hot climates support this statement.

Diets high in fat appear to become increasingly unpalatable in hot climates, at least to Americans. Although trustworthy evidence regarding fat requirements is scarce, it appears safe to restrict the dietary intake of fat to low levels. On the other hand, contrary to the reaction of many Americans, the Latin Americans and the peoples of the Mediterranean basins for generations have eaten large amounts of vegetable oils without apparent ill effects.

The author states that there has been considerable overemphasis of the supposed beneficial effects of extra glucose as a prophylaxis against heat exhaustion. He found, in fact, that the administration of extra glucose during work produced some undesirable symptoms such as gastric uneasiness.

There is no doubt that the requirements for certain inorganic nutrients are higher in hot than in temperate climates, but of the essential salts only sodium chloride, apparently, is ever lost rapidly enough in amounts large enough to lead to deficiency states. Experimental studies have shown that continued depletion of salt results in poor performance, a disposition to heat exhaustion, and finally the better recognized stage of heat cramps. Men working in hot climates need approximately 15 to 20 g. of sodium chloride a day, but precise figures depend on the amount of sweat lost and its composition, which varies with activity and diet. Salt is best taken with food, but under extreme conditions, or when men abstain from eating, salt should be added to the drinking water in concentrations not higher than 0.2 per cent. Johnson found that taking salt tablets was definitely undesirable because a high percentage of men developed gastric distress after their use. Furthermore, the use of excessive amounts of salt is to be deprecated since this abnormally increases the requirement for water, and has been found to be associated with poor performance in the heat. A single day's severe work in hot climates does not deplete the salt reserves to the point of producing inefficiency. There is therefore no urgent need to replace salt while work is going on as there is in the case of water.

The controversial subject of needs for vitamins in hot climates has already been discussed in this journal (*Nutrition Reviews* **1**, *355* (*1943*)). It has been pointed out that the evidence as to any extensive loss of vitamins in the sweat of men performing work under conditions of great heat is not yet convincing. Johnson's experiments are consistent with this view. He states that until much more evidence is available it seems wise to conclude that requirements for water soluble vitamins are not higher in hot environments than present National Research Council standards.

These observations do not deny the importance of attention to the diet in tropical climates. Critical factors which must be considered in planning an emergency ration for short periods are water, calories, sodium chloride, carbohydrate, and vitamin B-complex, but in addition, to insure consumption of the planned diet, a particularly tempting and palatable meal demands more attention in tropical climates.

VITAMIN DEFICIENCIES AND SULFONAMIDES

A subject which has received a great deal of attention during the past few years is the production of vitamin deficiencies in rats by the inclusion of sulfonamides in purified diets. Several publications in this field have been reviewed (*Nutrition Reviews* **1**, *35*, *175*, *341* (*1942–43*); **2**, *54* (*1944*)). Investigations recently described have brought to six the number of specific deficiency syndromes produced in this way and identified. Five of these deficiencies have been prevented or corrected by the specific vitamin involved. The sixth deficiency, pantothenic acid, is said to be corrected by this vitamin when produced by sulfapyridine under conditions described by West, Jefferson, and Rivera (*J. Nutrition* **25**, *471* (*1943*)), but not when produced by succinylsulfathiazole under other experimental conditions (Wright and Welch, *Science* **97**, *426* (*1943*); *J. Nutrition* **27**, *55* (*1944*)).

The first deficiency identified was that of vitamin K. Black, Overman, Elvehjem, and Link (*J. Biol. Chem.* **145**, *137* (*1942*)) described a prolongation of prothrombin time when sulfaguanidine or succinylsulfathiazole was added to a synthetic diet and prevention of this effect by the administration of vitamin K. Welch and Wright (*J. Nutrition* **25**, *555* (*1943*)) and Day, Wakin, Krider, and O'Banion (*Ibid.* **26**, *585* (*1943*)) have presented confirmatory data.

The production of a biotin deficiency in rats receiving sulfonamides was described by Daft, Ashburn, and Sebrell (*Science* **96**, *321* (*1942*)), and was found independently by Nielsen and Elvehjem (*J. Biol. Chem.* **145**, *713* (*1942*)) and by Martin (*Proc. Soc. Exp. Biol. Med.* **51**, *353* (*1942*)).

Hyalinization, necrosis, and calcification of voluntary muscle occurring in rats receiving succinylsulfathiazole in purified diets was found to be preventable by alpha-tocopherol by Daft, Endicott, Ashburn, and Sebrell (*Ibid.* **53**, *130* (*1943*)). Other investigators have employed diets containing larger amounts of vitamin E and have not reported muscle lesions.

Nielsen and Black (*Ibid.* **55**, *14* (*1944*)) have reported the occurrence of an alopecia in rats receiving succinylsulfathiazole in a purified diet supplemented by thiamin, riboflavin, pyridoxine, pantothenic acid, choline, vitamin K, halibut liver oil, biotin, and a "folic acid" concentrate. This alopecia could be prevented or cured by inositol.

Leucopenia, granulocytopenia, and anemia have occurred in rats receiving sulfanilamide, sulfathiazole, or sulfadiazine (Kornberg, Daft, and Sebrell (*Science* **98**, *20* (*1943*)), as well as in those receiving sulfaguanidine or succinylsulfathiazole (Spicer, Daft, Sebrell, and Ashburn (*Pub. Health Reports* **57**, *1559* (*1942*)). It was noted by these investigators and by others that these blood dyscrasias could be prevented or corrected by concentrates prepared from liver and containing "folic acid," but no positive identification of the active principle could, of course, be made until it was obtained in a pure state. Following the isolation of crystalline "vitamin Bc" by Pfiffner *et al.* (*Science* **97**, *404* (*1943*)) and of a crystalline "growth factor for Lactobacillus casei" by Stokstad (*J. Biol. Chem.* **149**, *573* (*1943*)), these materials were tested in rats and were found to correct the blood dyscrasias (Daft and Sebrell, *Pub. Health Reports* **58**, *1542* (*1943*)). The term "folic acid" has been used by many investigators to designate any one of several substances possessing similar biologic properties, among them being the "vitamin Bc" of Pfiffner *et al.*, and the "growth factor for Lactobacillus casei" of Stokstad. This loose terminology is open to criticism but will perhaps suffice until the chemical structures of the different compounds have been established.

West, Jefferson, and Rivera (*J. Nutrition* **25**, *471* (*1943*)) fed rats a diet containing 6 per cent of casein, 1 per cent of sulfapyri-

dine, and a daily individual supplement of 0.4 g. of brewers' yeast. They noted hemorrhagic necrosis of the adrenals, "blood-caked" whiskers, alopecia, and a slight dermatitis. A further daily supplement of 1 mg. of calcium pantothenate or an increase of the yeast to 1.2 g. caused the disappearance of the deficiency symptoms. These observations seem convincing even though no confirmation from other laboratories has as yet appeared.

Wright and Welch reported the production of a pantothenic acid deficiency in rats which is not reversible by the administration of pantothenic acid, either orally or parenterally. Black rats fed purified diets containing 2 per cent of succinylsulfathiazole and receiving amounts of pantothenic acid in considerable excess of accepted requirements developed alopecia, spectacled eyes, ophthalmitis, porphyrin-caked whiskers, and achromotrichia. These manifestations were accompanied by a low concentration of pantothenic acid in the liver. For purposes of comparison, Wright and Welch analyzed the livers of rats receiving different types of diets for biotin, "folic acid," and pantothenic acid. Rats on a stock ration served as controls and no effect on the vitamin levels in the liver was noted from the inclusion of 10 per cent of succinylsulfathiazole in this diet. After rats had received purified rations without drug, supplemented by thiamin, riboflavin, pyridoxine, pantothenic acid, niacin, p-aminobenzoic acid, inositol, and vitamin K, the livers were found to be low in biotin and very low in "folic acid." No frank deficiency signs were evident. The inclusion of 2 per cent of succinylsulfathiazole in the purified diets caused a rather small further decrease in the levels of biotin and "folic acid," and a drop in the pantothenic acid level from a control value of about 80 micrograms per gram to about 40 micrograms per gram of fresh tissue. This was shown to represent a deficiency level. Achromotrichia, porphyrin-caked whiskers, and other deficiency signs appeared. Administration of large amounts of pantothenic acid, either orally or parenterally, caused neither a remission of the deficiency signs nor an increase in the liver level of the vitamin. When crystalline biotin and a "folic acid" concentrate were given, however, there was a marked improvement in the general condition of the animals and the pantothenic acid content of the livers rose to the same level as that found in rats on a stock ration.

Wright and Welch interpret these data as demonstrating a failure in the utilization of pantothenic acid, this utilization being restored by the simultaneous administration of biotin and "folic acid" (or some other constituent of the "folic acid" concentrate employed).

This interpretation is an extremly interesting one. Some objections remain to be answered, however, and another interpretation of at least a part of the data is possible. Adrenal hemorrhages have been reported to be among the most prominent signs of pantothenic acid deficiency (Unna, Richards, and Sampson, *J. Nutrition* **22**, *553* (*1941*)), yet such hemorrhages were not reported as occurring in these experiments. Their absence would argue against a complete failure of pantothenic acid utilization. The deficiency signs noted clinically are known to be nonspecific and, while suggestive, are not conclusive. Martin in an earlier communication (*Proc. Soc. Exp. Biol. Med.* **51**, *353* (*1942*)) reported the graying of rats receiving sulfaguanidine and noted the chromotrichial activity of a "folic acid" concentrate. He interpreted his results as indicating that "folic acid" as well as pantothenic acid is a chromotrichial factor. It is to be hoped that further work will clarify this controversial point.

It is evident that the use of sulfonamides in purified diets has been an extremely valuable tool for the production and study of vitamin deficiencies. Its usefulness promises to continue.

NOTES

Letters to the Editor

Dear Sir:

I have found Nutrition Reviews so useful that I hesitate to send you what might seem to be a criticism of one of the articles.

The review "Crystalline Folic Acid and Agranulocytosis" appears in the current volume, page 103. Since folic acid is the center of interest, I would like to know what compound the reviewer has in mind, where Daft and Sebrell got it, and how they knew they had folic acid. The crystallization of folic acid would be an important event, but I have not seen it announced.

Almquist (*Proc. Soc. Exp. Biol. Med.* **54**, *58* (*1943*)) says the *original* folic acid is multiple.

Elvehjem (*Proc. Inst. Med. Chicago* **14**, *486* (*1943*)) mentions two factors distinct from *true* folic acid.

Elvehjem *et al.* (*J. B. C.* **148**, *163* (*1943*)) found no evidence that the chick requires folic acid, though his paper is not directed to that point. He mentioned two other substances that are required.

Keresztesy *et al.* (*Science* **97**, *465* (*1943*)) have isolated a new substance which resembles the Williams factor if assayed by L. casei, but not if assayed with S. lactis R.

Stokstad (*J. B. C.* **149**, *573* (*1943*)) obtained preparations from yeast and liver which seemed identical if assayed with L. casei ϵ, but the preparation from yeast was one-half as active as the one from liver if assayed with S. lactis R. Apparently both are different from the one isolated by Keresztesy *et al.*

Hutchings, Stokstad, Bohonos, and Slobodkin (*Science* **99**, *371* (*1944*)) have isolated another Lactobacillus casei factor which is "active in the nutrition of the chick." It is "85 to 90 per cent as active as that from liver when assayed with L. casei, but only 6 per cent as active as the liver compound by S. lactis R. assay."

The italics are mine in the above comments. If we have an original folic acid, a true folic acid, and substances that resemble folic acid, which did your reviewer have in mind? So far as I am aware none of the investigators of folic acid had satisfactory evidence that he was describing a pure compound.

Yours sincerely,
A. G. Hogan,
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Columbia, Mo.

The Coming Soybean

In addition to the development of soya products for foreign use, attention has been given by the federal government to the introduction of soya products for domestic use (Leaming, *J. Am. Dietet. Assn.* **19**, *824* (*1943*)). Three hundred million pounds of soya flour, flakes, and grits have been made available for use in home and institutional recipes, as well as in commercial formulas for such prepared foods as pancake and muffin mixes, cereal products, macaroni and other paste goods, meat products, soups, and breads. The 300 million pounds of soya products planned for domestic use represent about 140 million pounds of high quality and low cost protein, as well as substantial amounts of vitamins of the B-complex, and certain minerals, primarily iron, phosphorus, and calcium. This is a full year's requirement of protein for more than 2 million people. In introducing these new products, the Bureau of Human Nutrition and Home Economics of the Agricultural Research Administration, U. S. Department of Agriculture, has published a concise, attractive leaflet, "Cooking with Soya Flour and Grits," which is a direct result of intense work with the various available soya products and contains 37 carefully tested recipes.

Vitamin Losses in Cooking

The losses of ascorbic acid during cooking have been studied extensively, but less attention has been given to other vitamins. Cheldelin, Woods, and Williams (*J. Nutrition* **26,** *477 (1943)*) have now studied the losses of riboflavin, niacin, pantothenic acid, biotin, inositol, and "folic acid" which occur in the cooking of vegetables, fruits, milk, eggs, meat, and fish. The microbiologic assay methods developed in the University of Texas laboratories have been employed throughout. The authors point out that in certain cases the vitamins may have become "bound" by cooking and thus rendered unavailable to microorganisms or to the reagents used in various chemical tests, but still may be available for animal nutrition. Thus vitamin losses which appear to be large warrant reexamination at a later time.

In summary, riboflavin was destroyed in variable amounts in the presence of light, but there were negligible losses in the dark. In general, the losses were slight for niacin. Moderate to slight losses of pantothenic acid occurred in vegetables with losses up to one-third in meats. For biotin, there were moderate to negligible losses in vegetables, but losses up to 72 per cent in meats. The loss of inositol was generally moderate among meats, with steamed samples only slight. However, a loss up to 95 per cent occurred in vegetables, especially in legumes. The loss of "folic acid" was great in most foods.

The Protein of Peas

Among the vegetables, the legumes constitute the most important source of protein. Woods, Beeson, and Bolin (*J. Nutrition* **26,** *327 (1943)*) have studied the value of the Alaska field pea as the sole source of protein in a young rat's diet. Baking and autoclaving of the peas decreased the value for growth when compared with raw peas. The loss of protein value after such processing could be replaced by the addition of approximately one-half per cent of cystine or methionine. The authors conclude that peas are an excellent source of amino acids essential to the rat with the exception of methionine, and that processing destroys cystine. The supplementing effect of cystine to a low methionine diet has been explained by Mitchell (*Ann. Rev. Biochem.* **7,** *353 (1938)*) as due to the need of the animal for both amino acids, the cystine portion of which can be met by cystine itself or by synthesis from methionine.

The Average American Diet

An indication of the proportions of riboflavin, niacin, and pantothenic acid contributed by foods as prepared and cooked in the average American diet may be gained from the report of Cheldelin and Williams (*J. Nutrition* **26,** *417 (1943)*). These workers have assayed foods in proportions corresponding to the annual per capita consumption of each in the period 1934 to 1937. The principal contributions of riboflavin, in their order of importance, came from milk, white bread, eggs, potatoes, and liver. Beef, lean pork, fish, and white bread contributed niacin heavily, and for pantothenic acid, white bread, milk, eggs, and potatoes were important sources. The riboflavin, nicotinic acid, and pantothenic acid contents of the average American diet were approximately 1.4 mg., 11 mg., and 4.9 mg., respectively, per 2500 calories. These values are appreciably lower than the estimated daily requirements. Enrichment of bread and flour to meet the prevailing standard increases the level of riboflavin 12 per cent, to 1.6 mg.; that of nicotinic acid, 53 per cent, to 17 mg.

Tables are presented to permit the calculation of vitamin content of other foods.

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The Nutrition Foundation was organized by food and related manufacturers to develop and support a comprehensive research and educational program in the science of nutrition. It functions chiefly through grants in support of research in university centers where there are strong graduate schools in the basic sciences. Nutritional problems of immediate importance in relation to the war emergency receive special consideration.

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